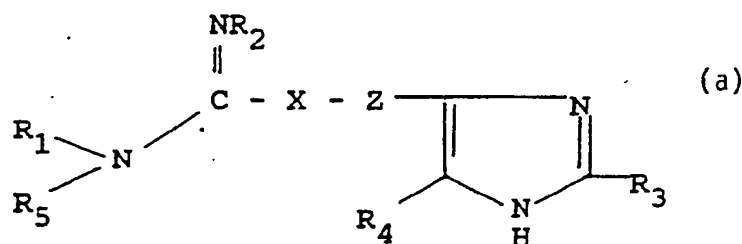




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| <b>(21) International Application Number:</b> PCT/NL92/00041<br><b>(22) International Filing Date:</b> 27 February 1992 (27.02.92)<br><b>(30) Priority data:</b><br>9100365 27 February 1991 (27.02.91) NL<br>9101764 22 October 1991 (22.10.91) NL<br><b>(71) Applicant (for all designated States except US):</b> SEED CAPITAL INVESTMENT (SCI) B.V. [NL/NL]; Bernadottelaan 15, NL-3527 GA Utrecht (NL).<br><b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only) :</b> TIMMERMAN, Hendrik [NL/NL]; De Savorin Lohmanplantsoen 3, NL-2253 VM Voorschoten (NL). VAN DER GOOT, Hendrikus [NL/NL]; Grote Belt 193, NL-2133 GW Hoofddorp (NL). |           | <b>(74) Agent:</b> HOIJTINK, Reinoud; Arnold & Siedsma Octrooibureau, Sweelinckplein 1, NL-2517 GK The Hague (NL).<br><br><b>(81) Designated States:</b> AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), U.S.<br><br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |

**(54) Title:** IMIDAZOLE-DERIVATIVES HAVING AGONISTIC OR ANTAGONISTIC ACTIVITY ON THE HISTAMINE H<sub>3</sub>-RECEPTOR

**(57) Abstract**

The invention relates to imidazole-derivatives of general formula (a). The invention in particular relates to derivatives having agonistic or antagonistic activity on the histamine H<sub>3</sub>-receptor. The novel imidazole-derivatives are isothio urea-, guanidine- and amidine-derivatives. The invention further relates to pharmaceutical compositions comprising the novel imidazole-derivatives as well as to methods for preparing the derivatives and for preparing pharmaceutical compositions having antagonistic and agonistic activity on the histamine H<sub>3</sub>-receptor.

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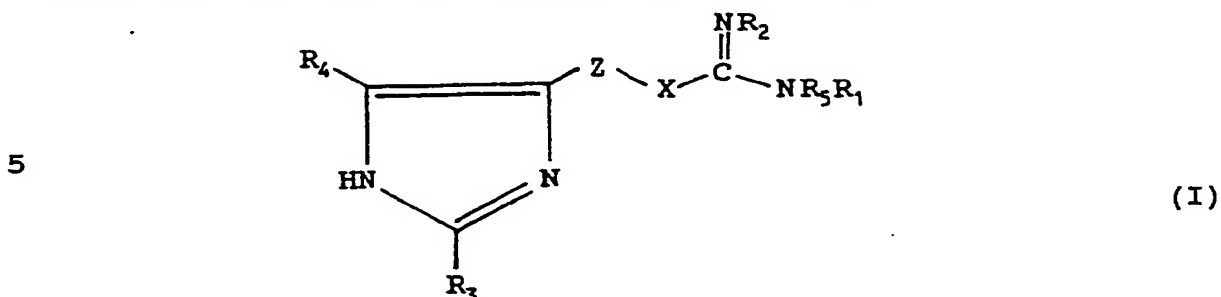
Imidazole-derivatives having agonistic or antagonistic activity on the histamine  $H_3$ -receptor.

The invention relates to novel imidazole-derivatives. The invention in particular relates to novel imidazole-derivatives having agonistic or antagonistic activity on the histamine  $H_3$ -receptor. More in particular it relates to isothioureia-, guanidine- and amidine-derivatives. The invention further relates to the synthesis of such compounds, a pharmaceutical composition comprising such compounds or pharmacological acceptable salts thereof, the use of the compounds as agents having biological activity, as agents with agonistic or antagonistic activity on the histamine  $H_3$ -receptor or for preparing a pharmaceutical composition.

In addition to the already longer known histamine  $H_1$ - and  $H_2$ -receptors there is also a third type histamine-receptor present in the human body, the so-called  $H_3$ -receptor. The  $H_3$ -receptor is a presynaptic receptor, i.e. it is located on a cell releasing histamine and stimulation of the receptor leads to inhibition of the histamine-release. Furthermore stimulation of the  $H_3$ -receptor influences also the release of other neurotransmitters, such as e.g. serotonin and acetylcholine.  $H_3$ -receptors are located in the central and peripheral nervous system, the lung tissue, the intestine and probably also in the spleen, the skin and the gastro-intestinal tract. A number of compounds having an effect on  $H_3$ -receptors has already been described. For a review see Schwartz et al., Agents and Actions 30, 1/2 (1990) p. 13-23.

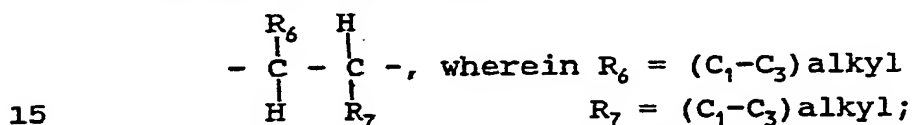
Chemical compounds can stimulate or inhibit the histamine  $H_3$ -receptor (Timmerman, J. Med. Chem. 33, p. 4-11 (1990)). Now a group of new imidazole-derivatives showing an agonistic or antagonistic activity on the histamine  $H_3$ -receptors has been found.

These derivatives are represented by the general formula:



10 wherein:

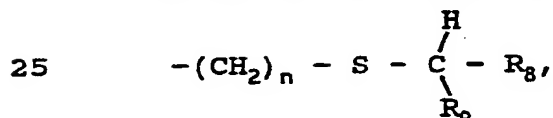
Z is a group of the formula (CH<sub>2</sub>)<sub>m</sub>, wherein m = 1-5 or a group of the formula:



wherein Z may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X represents S, NH or CH<sub>2</sub>;

20 R<sub>1</sub> represents hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl-, aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl-, wherein aryl may optionally be substituted, aryl, (C<sub>5</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl-, or a group of the formula:



wherein n = 1-4, R<sub>8</sub> is aryl, aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl-, (C<sub>5</sub>-C<sub>7</sub>)cycloalkyl- or (C<sub>5</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl- and R<sub>9</sub> is hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl- or aryl;

30 R<sub>2</sub> and R<sub>5</sub> represent hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

R<sub>3</sub> represents hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

R<sub>4</sub> represents hydrogen, amino-, nitro-, cyano-, halogen, 35 (C<sub>1</sub>-C<sub>3</sub>)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, sub-

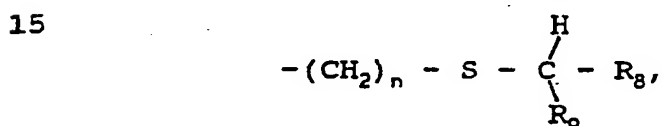
stituted naphthyl, pyridyl or substituted pyridyl; or pharmacological acceptable salts thereof.

Of these compounds the imidazole-derivatives of formula I wherein:

5 A) when Z is a group of the formula  $(CH_2)_m$ , wherein  $m = 1-5$ , and

1) when X is S,

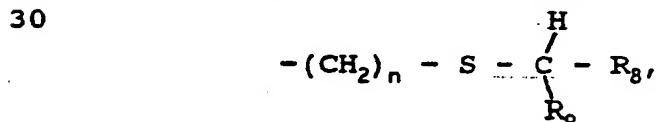
10  $R_1$  represents  $(C_1-C_3)$ alkyl- or aryl( $C_1-C_{10}$ )alkyl-, wherein aryl may optionally be substituted, when  $m = 1$  or 5, or  $(C_2-C_3)$ alkyl- or aryl( $C_2-C_{10}$ )alkyl-, wherein aryl may optionally be substituted, when  $m = 2, 3$  or 4; aryl,  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl-, or a group of the formula:



wherein  $n = 1-4$ ,  $R_8$  is aryl, aryl( $C_1-C_{10}$ )alkyl-,  $(C_5-C_7)$ cycloalkyl- or  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl- and  $R_9$  is hydrogen,  $(C_1-C_{10})$ alkyl- or aryl;  $R_2$  represents hydrogen,  $(C_1-C_3)$ alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; and

25  $R_3, R_4$  and  $R_5$  represent hydrogen; or 2) when X is NH,

$R_1$  represents hydrogen,  $(C_1-C_3)$ alkyl-, aryl, aryl( $C_1-C_{10}$ )alkyl-, wherein aryl may optionally be substituted,  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl-, or a group of the formula:



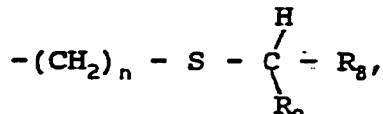
wherein  $n = 1-4$ ,  $R_8$  is aryl, aryl( $C_1-C_{10}$ )alkyl-,  $(C_5-C_7)$ cycloalkyl- or  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl- and  $R_9$  is hydrogen or  $(C_1-C_{10})$ alkyl-;  $R_2$  represents hydrogen,  $(C_1-C_3)$ alkyl-, aryl or arylalkyl-, wherein aryl may be optionally substituted

tuted; and

$R_3$ ,  $R_4$  and  $R_5$  represent hydrogen; or

3) when X is  $\text{CH}_2$ ,

$R_1$  represents hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ ,  
 5 aryl $(\text{C}_1\text{-C}_{10})\text{alkyl-}$ , wherein aryl may optionally be  
 substituted, aryl,  $(\text{C}_5\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_{10})\text{alkyl-}$ ,  
 or a group of the formula:



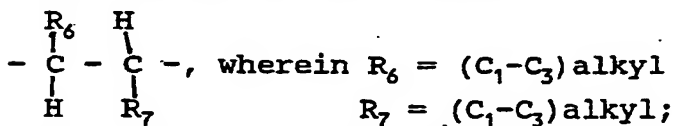
10 wherein  $n = 1\text{-}4$ ,  $R_8$  is aryl, aryl $(\text{C}_1\text{-C}_{10})\text{alkyl-}$ ,  
 $(\text{C}_5\text{-C}_7)\text{cycloalkyl-}$  or  $(\text{C}_5\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_{10})\text{alkyl-}$   
 and  $R_9$  is hydrogen,  $(\text{C}_1\text{-C}_{10})\text{alkyl-}$  or aryl;

$R_2$  and  $R_5$  represent hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ , aryl or  
 15 arylalkyl-, wherein aryl may optionally be substi-  
 tuted;

$R_3$  represents hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl}$ , aryl or  
 arylalkyl-, wherein aryl may be substituted; and

$R_4$  represents hydrogen, amino-, nitro-, cyano-,  
 20 halogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ , aryl or arylalkyl-,  
 wherein aryl may optionally be substituted;

B) when Z is a group of the formula :

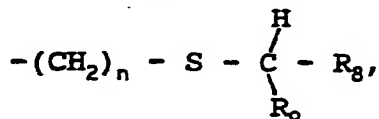


$\text{R}_7 = (\text{C}_1\text{-C}_3)\text{alkyl};$

25 wherein Z may optionally comprise other substituents  
 selected such that the activity of the derivative is not  
 negatively affected,

X represents S, NH or  $\text{CH}_2$ ;

30  $R_1$  represents hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ ,  
 aryl $(\text{C}_1\text{-C}_{10})\text{alkyl-}$ , wherein aryl may optionally be  
 substituted, aryl,  $(\text{C}_5\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_{10})\text{alkyl-}$ ,  
 or a group of the formula:



35 wherein  $n = 1 - 4$ ,  $R_8$  is aryl, aryl $(\text{C}_1\text{-C}_{10})\text{alkyl-}$ ,

(C<sub>5</sub>-C<sub>7</sub>)cycloalkyl- or (C<sub>5</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>10</sub>)alkyl- and R<sub>9</sub> is hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl- or aryl;

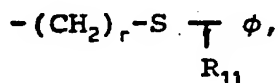
R<sub>2</sub> and R<sub>5</sub> represent hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; R<sub>3</sub> represents hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and R<sub>4</sub> represents hydrogen, amino-, nitro-, cyano-, halogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl, are novel derivatives.

Agonistic activity is in particular shown by compounds of formula I, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen, m is 2, and X is S or NH. The compound S-[2-(4-imidazolyl)ethyl]isothiourea shows a strong agonistic activity and is therefore preferred as the active ingredient in a pharmaceutical composition having histamine H<sub>3</sub>-agonistic activity.

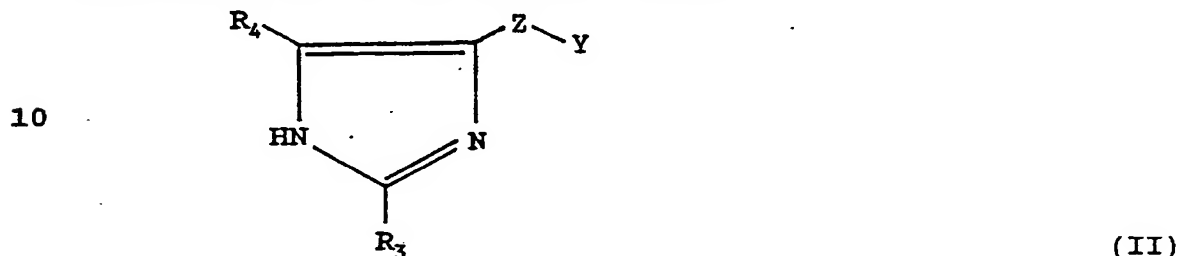
Antagonistic activity is in particular shown by compounds of formula I, wherein R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen; m is 2 or 3, R<sub>1</sub> is a group of the formula -(CH<sub>2</sub>)<sub>n</sub>R<sub>10</sub>, wherein R<sub>10</sub> is aryl or substituted aryl, n ≥ 1 and X is S or NH. Preferred compounds are S-[2-(imidazol-4-yl)ethyl]-N-(2-phenylethyl)-isothiourea, N-benzyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(2-phenylethyl)isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylethyl)isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylbutyl)isothiourea, S-[3-(4(5)-imidazolyl)propyl]-N-(4-chlorobenzyl)isothiourea, N-cyclohexylmethyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea and S-[3-(4(5)-imidazolyl)propyl]-N-(4-iodophenylethyl)isothiourea.

Other compounds showing strong antagonistic activity are compounds of formula I, wherein R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen, m is 1, 2 or 3; and R<sub>1</sub> is a group of the formula



wherein  $\phi$  is aryl,  $r$  is 1, 2 or 3; and  $R_{11}$  is hydrogen,  $(C_1-C_{10})$ alkyl- or aryl. A preferred compound is N-[2-(benzylthio)ethyl]-S-[3-(imidazol-4-yl)propyl]isothiourea.

Compounds of formula I can in general be synthesized in a for analogous compounds known manner. Favourable methods for synthesizing consist in condensation of a imidazole-compound of the general formula:



wherein  $Y$  represents Br, OH, or O-alkyl, with a thiourea-derivative having the general formula:



or condensation of a imidazole of formula II wherein  $Y$  represents  $\text{NH}_2$ , with a isothiourea-derivative having the general formula:



wherein in the formulas III and IV  $R$  represents hydrogen,  $(C_1-C_{10})$ alkyl-, aryl $(C_1-C_{10})$ alkyl- or aryl, and  $R_{12}$  represents  $(C_1-C_{10})$ alkyl. As solvents polair solvents are used such as ethanol or propanol. The condensations are carried out at temperatures between roomtemperature and the boiling point of the solvents for between 30 minutes and 10 hours.

Reactions take place in acid environment, e.g. hydrobromic acid, or in neutral environment. The obtained product can be processed in the usual way. If desired it is further possible to convert the obtained compounds of formula I in other compounds of formula I.



The following examples illustrate the synthesis of compounds of the present invention but are never intended to limit the scope thereof.

5

**EXAMPLE 1**

Synthesis of N-benzyl-S-[2-(imidazol-4-yl)ethyl]isothiurea dipicrate (VUF 9028).

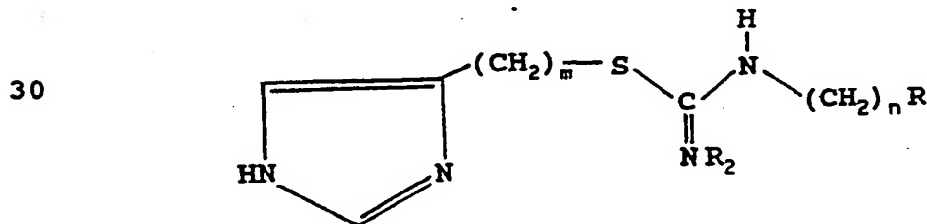
3.5 gram (13.7 mmol) 4(5)-(2-bromoethyl)imidazo-  
10 le.HBr and 2.3 gram N-benzylthiourea were refluxed for 60 hours in 30 ml ethanol. The ethanol was evaporated and the product was purified by means of column chromatography, using methanol/ethylacetate as eluent.

Subsequently the solvent was evaporated and the  
15 residue dissolved in methanol where to 10 gram picric acid in methanol was added. After addition of water an oil was formed, which after stirring with water became solid. The solid matter with melting point 166.9-169.8°C was subsequently filtrated. The NMR-results of this compound are  
20 given in table 1.

**EXAMPLE 2**

Synthesis of S-[3-(4(5)-imidazolyl)alkyl]-N-(2-(substituted)-arylalkyl)isothiurea-derivatives.

25 Analogous to the preparation method of VUF 9028 from example 1 a number of compounds were synthesized with the formula:



35 The meaning of n, m and R, the solvent of the condensation reaction and the melting points of the compounds are given in the table below. The NMR-results are given in table 1.

|    | Compound | R <sub>2</sub>  | R                                  | n | m | melt.point | salt    | solvent |
|----|----------|-----------------|------------------------------------|---|---|------------|---------|---------|
|    | VUF 8397 | H               | C <sub>6</sub> H <sub>5</sub>      | 0 | 2 | 174-176°C  | 2HBr    | 2-prop. |
| 5  | VUF 9029 | H               | C <sub>6</sub> H <sub>5</sub>      | 2 | 2 | 177-185°C  | 2HBr    | eth.    |
|    | VUF 9030 | H               | C <sub>6</sub> H <sub>5</sub>      | 3 | 2 | 152-155°C  | dipicr. | eth.    |
|    | VUF 9031 | H               | C <sub>6</sub> H <sub>5</sub>      | 4 | 2 | 136-139°C  | 2HBr    | eth.    |
|    | VUF 9051 | CH <sub>3</sub> | C <sub>6</sub> H <sub>5</sub>      | 2 | 2 | 152-156°C  | 2HBr    | eth.    |
|    | VUF 9107 | H               | C <sub>6</sub> H <sub>5</sub>      | 1 | 3 | 155-160°C  | 2HBr    | eth.    |
| 10 | VUF 9151 | H               | C <sub>6</sub> H <sub>5</sub>      | 2 | 3 | 178-183°C  | 2HBr    | eth.    |
|    | VUF 9152 | H               | C <sub>6</sub> H <sub>5</sub>      | 3 | 3 | 177-184°C  | 2HBr    | eth.    |
|    | VUF 9153 | H               | 4-ClC <sub>6</sub> H <sub>4</sub>  | 1 | 3 | 200-205°C  | 2HBr    | eth.    |
|    | VUF 9163 | H               | c-C <sub>6</sub> H <sub>11</sub>   | 1 | 3 | 137-153°C  | dipicr. | eth.    |
|    | VUF 4571 | H               | C <sub>6</sub> H <sub>5</sub>      | 4 | 3 | 112-134°C  | dipicr. | eth.    |
| 15 | VUF 4586 | H               | 4-IC <sub>6</sub> H <sub>4</sub> * | 2 | 3 | 188-190°C  | 2HBr    | 2-prop. |

\* Radioactively labeled compound, e.g. for use as a tracer-molecule

## 20 EXAMPLE 3

Synthesis of N-[2-(imidazol-4-yl)ethyl]-N'-phenyl guanidine dipicrate (VUF 9006).

### Step 1:

#### 25 Synthesis of S-ethyl-N-phenylisothiurea.

4 gram N-phenylisothiurea (33 mmol) and 5 ml ethylbromide were refluxed for 10 hours in ethanol. Again 5 ml ethylbromide was added. The reaction course was followed by thin layer chromatography (ethylacetate/petroleumether 3:7).

#### 30 Subsequently the solvent was evaporated and the residu crystallised from ethanol/ethylacetate.

### Step 2:

15 mmol histamine.2HCl was added to 30 mmol sodiummethanolate in ethanol (prepared by dissolving 30 mmol sodium in ethanol). Subsequently it was refluxed for one half hour, after which the mixture was cooled in ice and the formed NaCl was

filtrated.

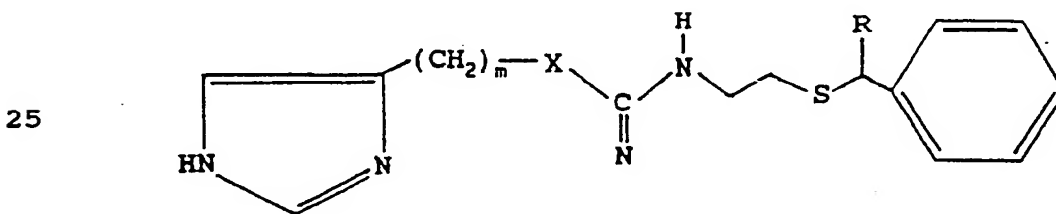
To the filtrate 15 mmol S-ethyl-N-phenylisothiourea was added. Next the reaction mixture was refluxed for 35 hours (control with thin layer chromatography (ethylacetate/ 5 petroleumether 1:1, saturated with ammonia)). Subsequently the solvent was evaporated and the residue dissolved in methanol. 35 mmol picric acid were added. The product was separated by the addition of water and was subsequently crystallised from methanol/water. The melting point was 10 235-238°C.

Analogous to the synthesis of VUF 9006 N-[2-(imidazol-4-yl)ethyl]-N'-phenyl-ethylguanidine dipicrate (VUF 9007; meltingpoint 196-198°C) was prepared. 15 The NMR-results are given in table 1.

#### EXAMPLE 4

Synthesis of N-[2-(arylalkylthio)alkyl]-S-[3-(imidazol-4-yl)alkyl]isothiourea- and -guanidine-derivatives.

20 Analogous to example 1 compounds were synthesized having the formula:



30 The meaning of the symbols m, X and R, the solvent of the condensation reaction and the melting points of the compounds are given in the table below. The NMR-results are given in table 1.

35

| Compounds  | m | X  | R                             | melting point | salt    | solvent |
|------------|---|----|-------------------------------|---------------|---------|---------|
| 5 VUF 8404 | 2 | S  | H                             | 233-235°C     | 2HBr    | 2-prop. |
| VUF 8405   | 3 | NH | H                             | 145-148°C     | dipicr. | ethanol |
| VUF 8409   | 2 | S  | C <sub>6</sub> H <sub>5</sub> | 106-109°C     | dipicr. | ethanol |
| VUF 8414   | 3 | S  | H                             | 126-133°C     | dipicr. | ethanol |

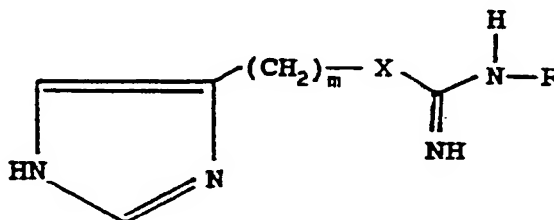
10

**EXAMPLE 5**

Synthesis of N-alkyl-S-[2-(4-imidazolyl)alkyl]isothioure-  
15 and -guanidine-derivatives.

Analogous to example 1 compounds were synthesized  
having the formula:

20



The meaning of the symbols m, X and R, the solvent of the  
25 condensation reaction and the melting points of the com-  
pounds are given in the table below. The NMR-results are  
given in table 1.

30

| Compound  | m | X  | R               | melting point | salt | solvent |
|-----------|---|----|-----------------|---------------|------|---------|
| VUF 8325  | 2 | S  | H               | 210-212°C     | 2HBr | eth.    |
| VUF 83100 | 2 | NH | H               | 222-223°C     | 2HCl | eth.    |
| VUF 8621  | 2 | S  | CH <sub>3</sub> | 180-181°C     | 2HBr | water   |

35

11/1

TABLE 1. NMR-results of the compounds mentioned in the description.

| <u>COMPOUNDS</u>   |                |           |            |    |
|--------------------|----------------|-----------|------------|----|
| <u>AGONISTS</u>    |                |           |            |    |
| 5                  | <u>VUF8325</u> |           |            |    |
|                    | 3.06 ppm       | triplet   | J = 7.0 Hz | 2H |
|                    | 3.56 ppm       | triplet   | J = 7.0 Hz | 2H |
|                    | 7.61 ppm       | singlet   |            | 1H |
|                    | 9.01-9.27 ppm  | multiplet |            | 5H |
| 10                 | <u>VUF8621</u> |           |            |    |
|                    | 2.93 ppm       | singlet   |            | 3H |
|                    | 3.07 ppm       | triplet   | J = 6.8 Hz | 2H |
|                    | 3.59 ppm       | triplet   | J = 6.8 Hz | 2H |
|                    | 7.60 ppm       | singlet   |            | 1H |
| 15                 | 9.11 ppm       | doublet   | J = 1.3 Hz | 1H |
| <u>ANTAGONISTS</u> |                |           |            |    |
|                    | <u>VUF9028</u> |           |            |    |
|                    | 3.06 ppm       | triplet   | J = 6.9    | 2H |
|                    | 3.54 ppm       | triplet   | J = 6.9    | 2H |
| 20                 | 4.58 ppm       | singlet   |            | 2H |
|                    | 7.29-7.49 ppm  | multiplet |            | 6H |
|                    | 7.52 ppm       | singlet   |            | 4H |
|                    | 8.62 ppm       | singlet   |            | 1H |
|                    | 9.08 ppm       | doublet   | J = 1.3 Hz | 1H |
| 25                 | <u>VUF9029</u> |           |            |    |
|                    | 2.90 ppm       | triplet   | J = 7.5 Hz | 2H |
|                    | 3.00 ppm       | triplet   | J = 7.0 Hz | 2H |
|                    | 3.50-3.69 ppm  | multiplet |            | 4H |
|                    | 7.21-7.35 ppm  | multiplet |            | 5H |
| 30                 | 7.58 ppm       | singlet   |            | 1H |
|                    | 9.16 ppm       | doublet   | J = 1.3 Hz | 1H |
|                    | <u>VUF9030</u> |           |            |    |
|                    | 1.86 ppm       | quintet   | J = 7.4 Hz | 2H |
|                    | 2.62 ppm       | triplet   | J = 7.4 Hz | 2H |
| 35                 | 3.05 ppm       | triplet   | J = 6.9 Hz | 2H |
|                    | 3.24-3.38 ppm  | multiplet |            | 2H |
|                    | 3.51 ppm       | triplet   | J = 6.9 Hz | 2H |
|                    | 7.16-7.39 ppm  | multiplet |            | 5H |
|                    | 7.53 ppm       | singlet   |            | 1H |
| 40                 | 8.61 ppm       | singlet   |            | 4H |
|                    | 9.06 ppm       | doublet   | J = 1.3 Hz | 1H |
|                    | <u>VUF9031</u> |           |            |    |
|                    | 1.45-1.71 ppm  | multiplet |            | 4H |
|                    | 2.60 ppm       | triplet   |            | 2H |
| 45                 | 3.05 ppm       | triplet   | J = 6.8 Hz | 2H |
|                    | 3.30-3.45 ppm  | multiplet |            | 2H |
|                    | 3.60 ppm       | triplet   | J = 6.8 Hz | 2H |
|                    | 7.13-7.46 ppm  | multiplet |            | 5H |
|                    | 7.60 ppm       | singlet   |            | 1H |
| 50                 | 9.13 ppm       | doublet   | J = 1.4 Hz | 1H |
|                    | <u>VUF9051</u> |           |            |    |
|                    | 2.80-3.06 ppm  | multiplet |            | 4H |
|                    | 3.50-3.68 ppm  | multiplet |            | 4H |
|                    | 7.18-7.40 ppm  | multiplet |            | 5H |
| 55                 | 7.57 ppm       | singlet   |            | 1H |
|                    | 9.09 ppm       | singlet   |            | 1H |

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|                |                |           |            |     |
|----------------|----------------|-----------|------------|-----|
| <u>VUF9006</u> |                |           |            |     |
|                | 2.90 ppm       | triplet   | J = 6.3 Hz | 2H  |
|                | 3.51 ppm       | triplet   | J = 6.3 Hz | 2H  |
|                | 7.14-7.50 ppm  | multiplet |            | 5H  |
| 5              | 7.69-7.86 ppm  | multiplet |            | 2H  |
|                | 8.59 ppm       | singlet   |            | 4H  |
|                | 8.97 ppm       | singlet   |            | 1H  |
| <u>VUF9007</u> |                |           |            |     |
|                | 2.74-2.92 ppm  | multiplet |            | 4H  |
| 10             | 3.32-3.51 ppm  | multiplet |            | 4H  |
|                | 7.18-7.50 ppm  | multiplet |            | 6H  |
|                | 8.63 ppm       | singlet   |            | 4H  |
|                | 9.05 ppm       | doublet   |            | 1H  |
| <u>VUF8404</u> |                |           |            |     |
| 15             | 2.66 ppm       | triplet   | J = 6.3 Hz | 2H  |
|                | 3.06 ppm       | triplet   | J = 6.3 Hz | 2H  |
|                | 3.40-3.72 ppm  | multiplet |            | 4H  |
|                | 3.81 ppm       | singlet   |            | 2H  |
|                | 7.28 ppm       | singlet   |            | 5H  |
| 20             | 7.58 ppm       | singlet   |            | 1H  |
|                | 9.07 ppm       | doublet   | J = 0.8 Hz | 1H  |
| <u>VUF8405</u> |                |           |            |     |
|                | 1.64 ppm       | quintet   | J = 7.2 Hz | 2H  |
|                | 2.38-2.84 ppm  | multiplet |            | 4H  |
| 25             | 3.06-3.56 ppm  | multiplet |            | 4H  |
|                | 3.80 ppm       | singlet   |            | 2H  |
|                | 7.26-7.44 ppm  | multiplet |            | 6H  |
|                | 8.60 ppm       | singlet   |            | 4H  |
|                | 9.02 ppm       | singlet   |            | 1H  |
| 30             | <u>VUF8409</u> |           |            |     |
|                | 2.56 ppm       | triplet   | J = 6.8 Hz | 2H  |
|                | 3.03 ppm       | triplet   | J = 6.8 Hz | 2H  |
|                | 3.26-3.70 ppm  | multiplet |            | 4H  |
|                | 5.40 ppm       | singlet   |            | 1H  |
| 35             | 7.10-7.56 ppm  | multiplet |            | 11H |
|                | 8.60 ppm       | singlet   |            | 4H  |
|                | 9.02 ppm       | singlet   |            | 1H  |
| <u>VUF8414</u> |                |           |            |     |
|                | 1.94 ppm       | quintet   | J = 6.8 Hz | 2H  |
| 40             | 2.60-2.94 ppm  | multiplet |            | 4H  |
|                | 3.20 ppm       | triplet   | J = 6.8 Hz | 2H  |
|                | 3.30-3.68 ppm  | multiplet |            | 2H  |
|                | 3.78 ppm       | singlet   |            | 2H  |
|                | 7.28-7.42 ppm  | multiplet |            | 6H  |
| 45             | 8.60 ppm       | singlet   |            | 4H  |
|                | 9.00 ppm       | doublet   | J = 1.0 Hz | 1H  |
| <u>VUF9107</u> |                |           |            |     |
|                | 1.86-2.05 ppm  | multiplet |            | 2H  |
|                | 2.76 ppm       | triplet   | J = 7.5 Hz | 2H  |
| 50             | 3.20-3.51 ppm  | multiplet |            | 7H  |
|                | 4.60 ppm       | singlet   |            | 2H  |
|                | 7.26-7.52 ppm  | multiplet |            | 6H  |
|                | 9.01 ppm       | doublet   | J = 1.3 Hz | 1H  |
| <u>VUF9151</u> |                |           |            |     |
| 55             | 1.81-1.98 ppm  | multiplet |            | 2H  |
|                | 2.73 ppm       | triplet   | J = 7.5 Hz | 2H  |

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|                |               |           |            |     |
|----------------|---------------|-----------|------------|-----|
|                | 2.89 ppm      | triplet   | J = 7.0 Hz | 2H  |
|                | 3.22 ppm      | triplet   | J = 7.0 Hz | 2H  |
|                | 3.34 ppm      | singlet   |            | 6H  |
|                | 3.52-3.68 ppm | multiplet |            | 2H  |
| 5              | 7.20-7.40 ppm | multiplet |            | 5H  |
|                | 7.48 ppm      | singlet   |            | 1H  |
|                | 9.02 ppm      | doublet   | J = 1.3 Hz | 1H  |
| <u>VUF9152</u> |               |           |            |     |
|                | 1.78-2.06 ppm | multiplet |            | 4H  |
| 10             | 2.64 ppm      | triplet   | J = 7.6 Hz | 2H  |
|                | 2.77 ppm      | triplet   | J = 7.3 Hz | 2H  |
|                | 3.19-3.50 ppm | multiplet |            | 10H |
|                | 7.18-7.40 ppm | multiplet |            | 5H  |
|                | 7.49 ppm      | singlet   |            | 1H  |
| 15             | 9.01 ppm      | doublet   | J = 1.3H   | 1H  |
| <u>VUF9153</u> |               |           |            |     |
|                | 1.86-2.06 ppm | multiplet |            | 2H  |
|                | 2.77 ppm      | triplet   | J = 7.2 Hz | 2H  |
|                | 3.22-3.49 ppm | multiplet |            | 6H  |
| 20             | 4.60 ppm      | singlet   |            | 2H  |
|                | 7.32-7.58 ppm | multiplet |            | 6H  |
|                | 9.04 ppm      | doublet   | J = 1.3H   | 1H  |
| <u>VUF9163</u> |               |           |            |     |
|                | 0.80-1.77 ppm | multiplet |            | 11H |
| 25             | 1.86-2.03 ppm | multiplet |            | 2H  |
|                | 2.74 ppm      | triplet   | J = 7.0 Hz | 2H  |
|                | 3.08-3.25 ppm | multiplet |            | 4H  |
|                | 3.35 ppm      | singlet   |            | 10H |
|                | 7.46 ppm      | singlet   |            | 1H  |
| 30             | 8.49 ppm      | singlet   |            | 4H  |
|                | 8.98 ppm      | doublet   | J = 1.3H   | 1H  |
| <u>VUF4571</u> |               |           |            |     |
|                | 1.47-1.70 ppm | multiplet |            | 4H  |
|                | 1.84-2.03 ppm | multiplet |            | 2H  |
| 35             | 2.42-2.66 ppm | multiplet |            | 50H |
|                | 2.74 ppm      | triplet   | J = 7.2 Hz | 2H  |
|                | 3.19 ppm      | triplet   | J = 7.2 Hz | 2H  |
|                | 3.26-3.38 ppm | multiplet |            | 2H  |
|                | 3.46 ppm      | multiplet |            | 10H |
| 40             | 7.11-7.35 ppm | multiplet |            | 5H  |
|                | 7.47 ppm      | singlet   |            | 1H  |
|                | 8.59 ppm      | singlet   |            | 4H  |
| <u>VUF4586</u> |               |           |            |     |
|                | 1.89 ppm      | multiplet |            | 2H  |
| 45             | 2.74 ppm      | triplet   | J = 7.2 Hz | 2H  |
|                | 2.83 ppm      | triplet   | J = 7.0 Hz | 2H  |
|                | 3.24 ppm      | multiplet |            | 2H  |
|                | 3.57 ppm      | multiplet | J = 7.2 Hz | 2H  |
|                | 7.05-7.20 ppm | multiplet |            | 2H  |
| 50             | 7.60-7.75 ppm | multiplet |            | 2H  |
|                | 7.50 ppm      | singlet   |            | 1H  |
|                | 9.03 ppm      | singlet   |            | 1H  |

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### Pharmacological experiments

The agonistics and antagonistics activities on the  $H_3$ -receptor of the various compounds were determined compared to histamine. The testmethods used therefor are described in  
5 Van der Werf et al., Agents and Actions 20, 3/4 (1987)  
p. 239-243 and Menkveld et al., European Journal of Pharmacology, 186 (1990) p. 343-347.

The results of the experiments are given in the tables below.  $pd_2$  is the negative logarithm of the concentration of the testcompound at which 50% agonistic activity  
10 was measured.  $pa_2$  is the negative logarithm of the concentration of the testcompound at which the concentration of the agonist had to be doubled to obtain the same effect as obtained when the antagonist was absent.

15       Pharmaceutical compositions, comprising compounds of formula I as defined in claim 19 as the active ingredient for therapeutically influencing the human and animal histaminergic system have the form of powders, suspensions, solutions, sprays, emulsions, unguents or creams and can be used  
20 for local application, intranasal, rectal, vaginal and also for oral or parenteral (intravenous, intradermal, intramuscular, intrathecal etc.) administration. Such compositions can be prepared by combining (i.e. by mixing, dissolving etc.) of the active compound of formula I in the form of a  
25 free acid or salt with pharmaceutically acceptable excipients with neutral character (such as aqueous or non-aqueous solvents, stabilizers, emulsifiers, detergents, additives), and further if necessary colouring agents and flavouring agents. The concentration of the active ingredient in a pharmaceutical  
30 composition can vary between 0.1% and 100%, depending on the nature of the influence and the method of administration. The dose of the active ingredient that is administered can further be varied between 0.1 mg and 100 mg per kg body-weight.



TABLE 2. Antagonistic activity

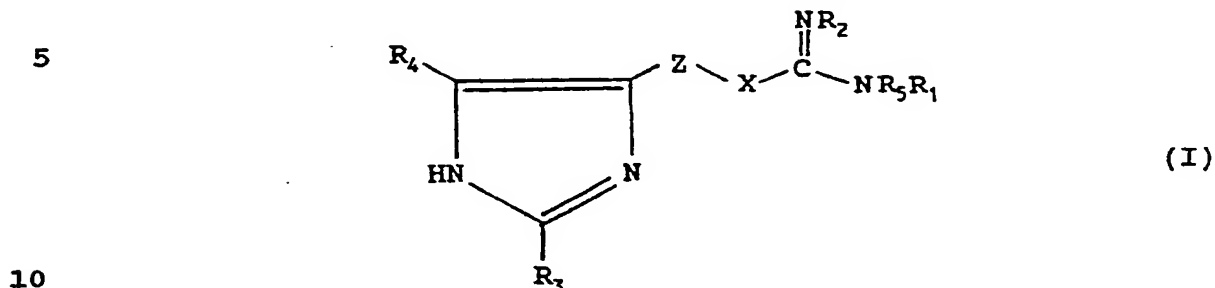
|    | Compound | pA <sub>2</sub> | testmethod       |
|----|----------|-----------------|------------------|
| 5  | VUF 8397 | 7.0             | ratcortex        |
|    | VUF 9028 | 7.8             | ileum guinea pig |
|    | VUF 9029 | 8.0             | ileum guinea pig |
|    | VUF 9030 | 7.6             | ileum guinea pig |
| 10 | VUF 9031 | 7.7             | ileum guinea pig |
|    | VUF 9051 | 7.8             | ileum guinea pig |
|    | VUF 9006 | 5.8             | ileum guinea pig |
|    | VUF 9007 | 6.3             | ileum guinea pig |
|    | VUF 8404 | 7.4             | ileum guinea pig |
| 15 | VUF 8405 | 7.9             | ileum guinea pig |
|    | VUF 8409 | 6.6             | ileum guinea pig |
|    | VUF 8414 | 8.6             | ileum guinea pig |
|    | VUF 9107 | 8.8             | ileum guinea pig |
|    | VUF 9151 | 8.8             | ileum guinea pig |
| 20 | VUF 9152 | 8.3             | ileum guinea pig |
|    | VUF 9153 | 9.9             | ileum guinea pig |
|    | VUF 9163 | 8.8             | ileum guinea pig |
|    | VUF 4571 | 8.4             | ileum guinea pig |
|    | VUF 4586 | 9.2             | ileum guinea pig |
| 25 |          |                 |                  |

TABLE 3. Agonistic activity

|    | Compound  | pD <sub>2</sub> | testmethod       |
|----|-----------|-----------------|------------------|
| 30 | VUF 8325  | 9.3             | ratcortex        |
|    | VUF 8325  | 8.1             | ileum guinea pig |
|    | VUF 83100 | 7.4             | ratcortex        |
|    | VUF 8621  | 7.3             | ileum guinea pig |
| 35 |           |                 |                  |

## C L A I M S

1. Imidazole-derivatives of the general formula:

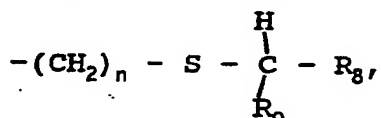


wherein:

A) when Z is a group of the formula  $(CH_2)_m$ , wherein  $m = 1-5$ ,  
and

1) when X is S,

15  $R_1$  represents  $(C_1-C_3)$ alkyl- or aryl( $C_1-C_{10}$ )alkyl-,  
wherein aryl may optionally be substituted, when  
 $m = 1$  or  $5$ , or  $(C_2-C_3)$ alkyl- or aryl( $C_2-C_{10}$ )  
alkyl-, wherein aryl may optionally be substitu-  
ted, when  $m = 2, 3$  or  $4$ ;  
20 aryl,  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl-, or a  
group of the formula:

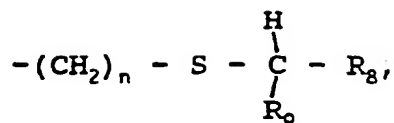


25 wherein  $n = 1-4$ ,  $R_8$  is aryl, aryl( $C_1-C_{10}$ )alkyl-,  
 $(C_5-C_7)$ cycloalkyl- or  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )al-  
kyl- and  $R_9$  is hydrogen,  $(C_1-C_{10})$ alkyl- or aryl;  
 $R_2$  represents hydrogen,  $(C_1-C_3)$ alkyl-, aryl or  
arylalkyl-, wherein aryl may optionally be substi-  
tuted; and

$R_3$ ,  $R_4$  and  $R_5$  represent hydrogen; or

2) when X is NH,

35  $R_1$  represents hydrogen,  $(C_1-C_3)$ alkyl-, aryl,  
aryl( $C_1-C_{10}$ )alkyl-, wherein aryl may optionally be  
substituted,  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl-, or a  
group of the formula:



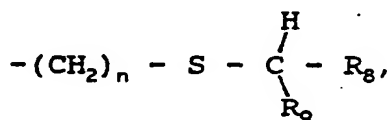
5 wherein  $n = 1-4$ ,  $R_8$  is aryl, aryl( $C_1-C_{10}$ )alkyl-, ( $C_5-C_7$ )cycloalkyl- or ( $C_5-C_7$ )cycloalkyl( $C_1-C_{10}$ )alkyl- and  $R_9$  is hydrogen or ( $C_1-C_{10}$ )alkyl-;

$R_2$  represents hydrogen, ( $C_1-C_3$ )alkyl-, aryl or arylalkyl-, wherein aryl may be optionally substituted; and

10  $R_3$ ,  $R_4$  and  $R_5$  represent hydrogen; or

3) when X is  $CH_2$ ,

$R_1$  represents hydrogen, ( $C_1-C_3$ )alkyl-, aryl( $C_1-C_{10}$ )alkyl-, wherein aryl may optionally be substituted, aryl, ( $C_5-C_7$ )cycloalkyl( $C_1-C_{10}$ )alkyl-,  
15 or a group of the formula:



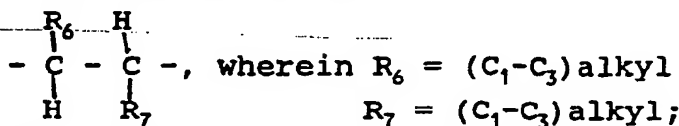
20 wherein  $n = 1-4$ ,  $R_8$  is aryl, aryl( $C_1-C_{10}$ )alkyl-, ( $C_5-C_7$ )cycloalkyl- or ( $C_5-C_7$ )cycloalkyl( $C_1-C_{10}$ )alkyl- and  $R_9$  is hydrogen, ( $C_1-C_{10}$ )alkyl- or aryl;

$R_2$  and  $R_5$  represent hydrogen, ( $C_1-C_3$ )alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

25  $R_3$  represents hydrogen, ( $C_1-C_3$ )alkyl, aryl or arylalkyl-, wherein aryl may be substituted; and

$R_4$  represents hydrogen, amino-, nitro-, cyano-, halogen, ( $C_1-C_3$ )alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted;

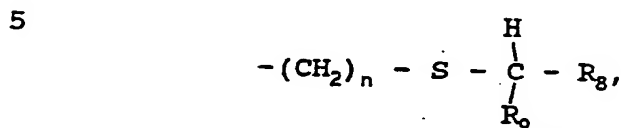
30 B) when Z is a group of the formula :



35 wherein Z may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X represents S, NH or  $CH_2$ ;

$R_1$  represents hydrogen,  $(C_1-C_3)$ alkyl-,  
 aryl( $C_1-C_{10}$ )alkyl-, wherein aryl may optionally be  
 substituted, aryl,  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl-,  
 or a group of the formula:



wherein  $n = 1 - 4$ ,  $R_8$  is aryl, aryl( $C_1-C_{10}$ )alkyl-,  
 $(C_5-C_7)$ cycloalkyl- or  $(C_5-C_7)$ cycloalkyl( $C_1-C_{10}$ )alkyl-  
 and  $R_9$  is hydrogen,  $(C_1-C_{10})$ alkyl- or aryl;

10  $R_2$  and  $R_5$  represent hydrogen,  $(C_1-C_3)$ alkyl-, aryl or  
 arylalkyl-, wherein aryl may optionally be substi-  
 tuted;  $R_3$  represents hydrogen,  $(C_1-C_3)$ alkyl, aryl or  
 arylalkyl-, wherein aryl may be substituted; and  
 15  $R_4$  represents hydrogen, amino-, nitro-, cyano-, halogen,  
 $(C_1-C_3)$ alkyl-, aryl or arylalkyl-, wherein aryl may  
 optionally be substituted;

wherein aryl is phenyl, substituted phenyl, naphthyl, sub-  
 stituted naphthyl, pyridyl or substituted pyridyl.

20 2. Imidazole-derivatives according to claim 1,  
 having the formula I, wherein  $R_3$ ,  $R_4$  and  $R_5$  are hydrogen;  
 $m$  is 2;  $R_1$  is a group of the formula  $(CH_2)_n R_{10}$  wherein  $R_{10}$  is a  
 substituted or non-substituted arylgroup,  $n \geq 1$ ; and  $X$  is S or  
 NH.

25 3. Imidazole-derivatives according to claim 2,  
 characterized in that  $R_2$  is hydrogen;  $m$  is 2; and  $X$  is S.

4. Imidazole-derivatives according to claim 3,  
 characterized in that the derivative is S-[2-(imidazol-4-yl)  
 ethyl]-N-(2-phenylethyl)isothiourea.

30 5. Imidazole-derivatives according to claim 2,  
 characterized in that  $R_2$  is hydrogen;  $m$  is 3; and  $X$  is S.

6. Imidazole-derivatives according to claim 5,  
 characterized in that the derivative is N-benzyl-S-[3-(4(5)-  
 imidazolyl)propyl]isothiourea.

35 7. Imidazole-derivatives according to claim 5,  
 characterized in that the derivative is S-[3-(4(5)-imidazo-  
 yl)propyl]-N-(2-phenylethyl)isothiourea.

8. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylpropyl)isothiourea.

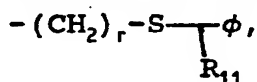
9. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(4-phenylbutyl)isothiourea.

10. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(4-chlorobenzyl)isothiourea.

11. Imidazole-derivatives according to claim 5, characterized in that the derivative is N-cyclohexylmethyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea.

12. Imidazole-derivatives according to claim 5, characterized in that the derivative is S-[3-(4(5)-imidazolyl)propyl]-N-(4-iodophenylethyl)isothiourea.

13. Imidazole-derivatives according to claim 1, having the formula I, wherein  $R_3$ ,  $R_4$  and  $R_5$  are hydrogenatoms; m is 1, 2 or 3;  $R_1$  is a group of the formula



wherein  $\phi$  is an arylgroup, r is 1, 2 or 3 and  $R_{11}$  is hydrogen,  $(C_1-C_{10})$ alkyl- or aryl.

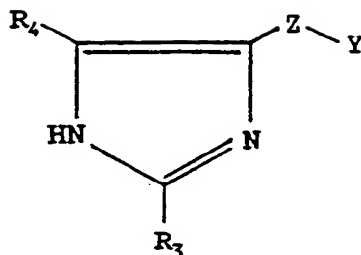
14. Imidazole-derivatives according to claim 13, characterized in that m is 3, r is 2,  $R_{11}$  is hydrogen and X is S or NH.

15. Imidazole-derivatives according to claim 14, characterized in that the derivative is N-[2-(benzylthio)ethyl]-S-[3-(imidazol-4-yl)propyl]isothiourea.

16. Method for preparing imidazole-derivatives, characterized in that compounds of formula I are being synthesized in a for analogous compounds known manner.

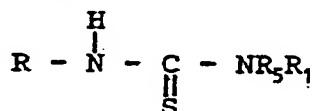
17. Method for preparing imidazole-derivatives, characterized in that compounds of formula I are prepared by condensation of an imidazole-derivative of the general formula:

18



(II)

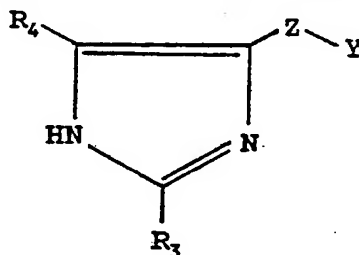
wherein Y represents Br, OH, or O-alkyl; and a thioureaderivative of the general formula:



(III)

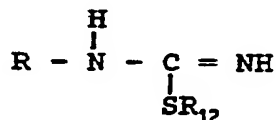
wherein R represents hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl- or aryl, and R<sub>12</sub> represents (C<sub>1</sub>-C<sub>10</sub>)alkyl-.

18. Method for preparing imidazole-derivatives according to claim 17, characterized in that compounds of formula I are being prepared by condensation of an imidazole-derivative of the general formula:



(II)

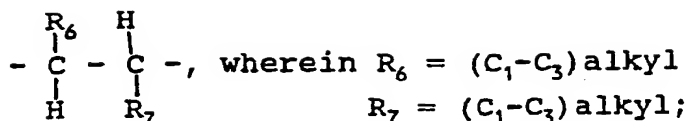
wherein Y represents NH<sub>2</sub>; and a thioureaderivative of the general formula



(IV)

19. Pharmaceutical composition having antagonistic or agonistic activity on the histamine H<sub>3</sub>-receptor, characterized in that it comprises as an active ingredient a compound of formula I, wherein :

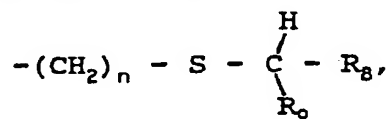
Z is a group of the formula (CH<sub>2</sub>)<sub>m</sub>, wherein m = 1-5 or a group of the formula:



wherein Z may optionally comprise other substituents  
 5 selected such that the activity of the derivative is not negatively affected,

X represents S, NH or  $\text{CH}_2$ ;

$\text{R}_1$  represents hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ ,  
 aryl $(\text{C}_1\text{-C}_{10})\text{alkyl-}$ , wherein aryl may optionally be sub-  
 10 stituted, aryl,  $(\text{C}_5\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_{10})\text{alkyl-}$ , or a group of the formula:



15 wherein  $n = 1\text{-}4$ ,  $\text{R}_8$  is aryl, aryl $(\text{C}_1\text{-C}_{10})\text{alkyl-}$ ,  $(\text{C}_5\text{-C}_7)\text{cycloalkyl-}$  or  $(\text{C}_5\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_{10})\text{alkyl-}$  and  $\text{R}_9$  is hydrogen,  $(\text{C}_1\text{-C}_{10})\text{alkyl-}$  or aryl;

$\text{R}_2$  and  $\text{R}_5$  represent hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ , aryl or arylalkyl-, wherein aryl may optionally be substituted;

20  $\text{R}_3$  represents hydrogen,  $(\text{C}_1\text{-C}_3)\text{alkyl}$ , aryl or arylalkyl-, wherein aryl may be substituted; and

$\text{R}_4$  represents hydrogen, amino-, nitro-, cyano-, halogen,  $(\text{C}_1\text{-C}_3)\text{alkyl-}$ , aryl or arylalkyl-, wherein aryl may optionally be substituted;

25 wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl; or pharmacological acceptable salts thereof.

20. Pharmaceutical composition according to claim 19, characterized in that it comprises as the active ingredient a compound of formula I or pharmacological acceptable salts thereof, wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  are hydrogen-  
 30 atoms; m is 2; and X is S or NH.

21. Pharmaceutical composition according to claim 20, characterized in that it comprises as the active ingredient S-[2-(4-imidazolyl)ethyl]isothiourea or a pharmacological acceptable salt thereof.  
 35

22. Pharmaceutical composition according to claim

19, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein  $R_3$ ,  $R_4$  and  $R_5$  are hydrogenatoms;  $m$  is 2;  $R_1$  is a group of the formula  $(CH_2)_n R_{10}$ , wherein  $R_{10}$  is a substituted or non-substituted aryl,  $n \geq 1$  and  $X$  is S or NH.

23. Pharmaceutical composition according to claim 22, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein  $R_2$  is hydrogen;  $m$  is 2; and  $X$  is S.

24. Pharmaceutical composition according to claim 23, characterized in that it comprises as the active ingredient S-[2-(imidazol-4-yl)ethyl]-N-(2-phenylethyl)isothiourea or a pharmacological acceptable salt thereof.

25. Pharmaceutical composition according to claim 23, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein  $R_2$  is hydrogen;  $m$  is 3; and  $X$  is S.

26. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative is N-benzyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmacological acceptable salt thereof.

27. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(2-phenylethyl)isothiourea or a pharmacological acceptable salt thereof.

28. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(3-phenylpropyl)isothiourea or a pharmacological acceptable salt thereof.

29. Pharmaceutical composition according to claim 25, characterized in that it comprises as the active ingre-



dient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(4-phenylbutyl)isothiourea or a pharmacological acceptable salt thereof.

30. Pharmaceutical composition according to claim 5 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(4-chlorobenzyl)isothiourea or a pharmacological acceptable salt thereof.

31. Pharmaceutical composition according to claim 10 25, characterized in that it comprises as the active ingredient the derivative N-cyclohexylmethyl-S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmacological acceptable salt thereof.

32. Pharmaceutical composition according to claim 15 25, characterized in that it comprises as the active ingredient the derivative S-[3-(4(5)-imidazolyl)propyl]-N-(4-iodophenylethyl)isothiourea or a pharmacological acceptable salt thereof.

33. Pharmaceutical composition according to claim 20 19, characterized in that it comprises as the active ingredient a compound of the formula I or pharmacological acceptable salts thereof, wherein  $R_3$ ,  $R_4$  and  $R_5$  are hydrogen;  $m$  is 1-3;  $R_1$  a group is of the formula  $-(CH_2)_r-S-\underset{R_{11}}{\overset{|}{T}}-\phi$  25 wherein  $\phi$  is aryl,  $r$  is 1, 2 or 3 and  $R_{11}$  is hydrogen,  $(C_1-C_{10})$ alkyl- or aryl.

34. Pharmaceutical composition according to claim 33, characterized in that  $m$  is 3,  $r$  is 2,  $R_{11}$  is hydrogen and  $X$  is S or NH.

30 35. Pharmaceutical composition according to claim 34, characterized in that it comprises as the active ingredient N-[2-(benzylthio)ethyl]-S-[3-(imidazole-4-yl)propyl]-isothiourea or a pharmacological acceptable salt thereof.

36. Use of compounds of formula I as defined in 35 claim 1 as an agent having biological activity.

37. Use of compounds of formula I as defined in claim 19 as an agent having agonistic or antagonistic acti-

vity on the histamine  $H_3$ -receptor.

38. Use of a compound of the formula I as defined in claim 19 for preparing a pharmaceutical composition having agonistic or antagonistic activity on the histamine  $H_3$ -5 receptor.

## INTERNATIONAL SEARCH REPORT

PCT/NL 92/00041

International Application No

|  |  |                                       |
|--|--|---------------------------------------|
| <b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>  |  |                                       |
| According to International Patent Classification (IPC) or to both National Classification and IPC  |  |                                       |
| Int.Cl. 5 C07D233/64;<br>C07D233/90;   | A61K31/415;<br>C07D233/68;   | C07D233/94;<br>C07D401/04;            |
| C07D233/95<br>C07D401/12   |  |                                       |
| <b>II. FIELDS SEARCHED</b>   |  |                                       |
| Minimum Documentation Searched <sup>7</sup>  |  |                                       |
| Classification System  | Classification Symbols   |                                       |
| Int.Cl. 5  | C07D ; A61K  |                                       |
| Documentation Searched other than Minimum Documentation<br>to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>  |  |                                       |
| <b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>  |  |                                       |
| Category <sup>10</sup>   | Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>   | Relevant to Claim No. <sup>13</sup>   |
| X  | DE,A,2 052 692 (SMITH KLINE & FRENCH<br>LABORATORIES LIMITED) 6 May 1971<br><br>see the whole document<br>---  | 1-9,<br>16-17,<br>19-29,<br>36-38     |
| X  | WO,A,8 707 891 (CEDONA PHARMACEUTICALS B.V.) 30<br>December 1987<br><br>see page 2<br>see page 4; example XII<br>see page 6, line 25 - line 31<br>---<br>-/- | 1,13-14,<br>18-19,<br>33-34,<br>36-37 |
| <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> |  |                                       |
| <b>IV. CERTIFICATION</b>   |  |                                       |
| Date of the Actual Completion of the International Search  | Date of Mailing of this International Search Report  |                                       |
| 17 JUNE 1992   | 30.07.92   |                                       |
| International Searching Authority  | Signature of Authorized Officer  |                                       |
| EUROPEAN PATENT OFFICE   | DE BUYSER I.A.F.   |                                       |

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| A  | EP,A,0 177 808 (KANTO ISHI PHARMACEUTICAL<br>CO., LTD) 16 April 1986<br>---  |                       |
| A  | EP,A,0 262 448 (HEUMANN PHARMA GMBH & CO) 6<br>April 1988<br>---   |                       |

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ON INTERNATIONAL PATENT APPLICATION NO. NL 9200041  
SA 57446**

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